Association of Methemoglobinemia and Intravenous Nitroglycerin Administration

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Significant elevation of arterial methemoglobin levels has been reported with the administration of intravenous (i.v.) nitroglycerin (NTG). To determine the incidence and clinical significance of this side effect of i.v. NTG, serial arterial methemoglobin levels were determined in 50 consecutive patients receiving i.v. NTG for 48 hours or longer. The mean i.v. NTG infusion rate was 290 ± 13 μg/min (4.1 ± 0.2 μg/kg/min) and the mean duration of infusion was 7.1 ± 0.5 days. The mean methemoglobin level for the 141 samples was 1.57 ± 0.08%, which differs from the control mean value in our laboratory of 0.44 ± 0.01%. Although no patient had clinical symptoms from methemoglobin, 20 patients had elevated (>1%) levels on at least 1 measurement. Seventy-eight of the 141 samples analyzed were in the normal range; 63 determinations were between 2 and 5%. Patients with normal methemoglobin levels differed from those with abnormal levels in the dose of i.v. NTG (mean infusion rate 244 ± 16 vs 351 ± 17 μg/min; total cumulative dose 1,612 ± 153 vs 3,398 ± 308 mg). Age, weight, renal and hepatic function, and arterial oxygen saturation were not different between the groups. In conclusion, clinically significant methemoglobinemia is uncommon with i.v. NTG infusion; however, when large doses of NTG are administered, this complication is more likely. (Am J Cardiol 1985;55:181–183)

Clinically significant methemoglobinemia during the administration of organic nitrates, including intravenous (i.v.) nitroglycerin (NTG), has been reported recently.[1–3] This oxidized (ferric) form of hemoglobin cannot bind or release oxygen and causes a leftward shift in the oxyhemoglobin dissociation curve.[4,5] We undertook a prospective study to determine the frequency and clinical significance of methemoglobinemia in patients treated with i.v. NTG.

Methods

Serial methemoglobin levels were measured in 50 consecutive patients treated with i.v. NTG for at least 48 hours. NTG in concentrations of either 300 or 600 μg/ml was infused through either polyvinyl chloride or polyethylene-polypropylene tubing. The infusion rate was controlled by an IMED volumetric infusion pump. The infusion rate was started at 25 to 50 μg/min and increased as tolerated at 25- to 50-μg/min increments to control angina pectoris.[6] Topical, oral and sublingual nitrates were administered as ordered by the attending physician.

Arterial blood samples were obtained 48 to 72 hours after NTG administration was initiated and repeated at 24- to 72-hour intervals during the duration of the infusion. Samples were collected in heparinized syringes and placed on ice for immediate transport to the blood gas laboratory, where they were analyzed on an IL 282 cooximeter for methemoglobin, expressed as percent (to the nearest whole number) of total hemoglobin present in the oxidized or methemoglobin state.

Results are expressed as mean ± standard error of the mean. Standard *t* tests were used to compare groups.

Results

The 50 patients in the study group included 26 men and 24 women, average age 63.6 ± 1.4 years. The indication for i.v. NTG was unstable angina in 11 patients (22%) and angina after myocardial infarction in 39 patients (78%). Intravenous NTG was administered continuously for a mean of 7.1 ± 0.5 days (range 1 to 30). The mean i.v. NTG infusion rate was 290 ± 13 μg/min (range 30 to 1,000) or 4.1 ± 0.2 μg/kg/min (range 0.4 to 12.6). In addition, 43 patients were receiving NTG ointment at a mean daily dosage of 18.0 ± 1.6 inches and 33 patients were receiving isosorbide dinitrate in a mean total oral dose of 299 ± 40 mg/day.

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EXHIBIT V

TABLE I Patient Characteristics

	Methemoglobin (0–1%) (n = 78)	Methemoglobin (2–5%) (n = 63)	p Value
Age (yr)	64 ± 1	65 ± 1	NS
Weight (kg)	76 ± 2	73 ± 1	NS
Creatinine (mg/dl)	1.2 ± 0.1	1.4 ± 0.1	<0.08
Blood urea nitrogen (mg/dl)	19 ± 0.9	20 ± 1.5	NS
Alk phos (mU/ml)	96 ± 3	105 ± 6	NS
Total bilirubin (mg/dl)	0.6 ± 0.04	0.4 ± 0.04	NS
PaO_2 (Torr)	74 ± 2	77 ± 2	NS
O_2 saturation (%)	94 ± 1	93 ± 1	NS

Alk phos = alkaline phosphatase; NS = not significant; PaO_2 = oxygen partial pressure.

TABLE II Nitrate Therapy

	Methemoglobin (0–1%)	Methemoglobin (2–5%)	p Valu
IV NTG μg/min	244 ± 16	351 ± 17	<0.00
μg/kg/min	3.2 ± 0.2	5.0 ± 0.3	<0.00
days	5.1 ± 0.3	9.7 ± 1.0	<0.00
mg (cumulative dose)	1,612 ± 153	3,398 ± 308	<0.00
NTG ointment (inches/day)	17 ± 1	20 ± 1	NS
Isosorbide dinitrate (mg/day)	295 ± 24	305 ± 33	NS

NS = not significant; NTG = nitroglycerin.

A total of 141 arterial samples were analyzed for methemoglobin. The mean methemoglobin level for these samples was 1.57 ± 0.08%, which is higher than the mean normal value for our laboratory, 0.44 ± 0.01%.[7] Abnormal methemoglobin levels are defined as more than 1%, which is the mean plus 2 standard deviations. Twenty patients had abnormal methemoglobin levels on at least 1 determination, but in no instance could clinical manifestations be attributed to this finding. Methemoglobin levels ranged from 0 to 5% of total hemoglobin (Fig. 1). Seventy-eight of the 141 samples were 0 or 1% and 63 determinations were between 2 and 5%.

In an attempt to identify the factors involved in the development of elevated methemoglobin, all blood samples were classified as having normal (≤1%) or abnormal (>1%) methemoglobin levels. The patients whose samples had normal methemoglobin levels were compared with those whose samples had abnormal methemoglobin levels. Age, weight, renal and hepatic function tests, and arterial oxygen saturation were not significantly different between the 2 groups (Table I). However, the i.v. NTG therapy at the time of sampling was different between the groups (Table II). The mean i.v. NTG infusion rate in patients with a normal methemoglobin level was 244 ± 16 μg/min, and that in patients with an elevated methemoglobin level was 351 ± 17 μg/min. The dose expressed in μg/kg/min was also significantly different. The duration of the i.v. NTG infusion was significantly longer in patients with abnormal methemoglobin levels, 9.7 ± 1.0 vs 5.1 ± 0.3 days. Predictably, the patients with elevated methemoglobin levels had a significantly greater total cumulative i.v. NTG dose (3,398 ± 308 mg) than those with normal levels (1,612 ± 153 mg). When the doses of NTG ointment or isosorbide dinitrate are compared, there is no significant difference between groups.

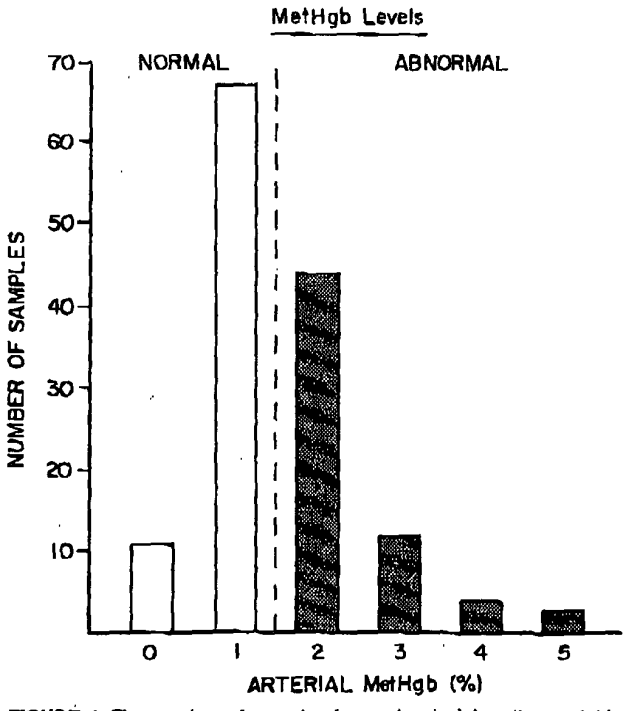

FIGURE 1. The number of samples for each arterial methemoglobin (MetHgb) level. The samples are divided into normal (0 to 1%) and abnormal (2 to 5%) values.

As the total cumulative dose of i.v. NTG increases, so does the percentage of samples with abnormal methemoglobin values (Fig. 2). For purposes of reference, a patient receiving a continuous infusion of 300 μg/min of NTG would receive approximately 450 mg/day.

After completion of the data collection for this study, a patient receiving i.v. NTG was found, in a routine arterial blood sample, to have a methemoglobin level of 12%. No clinical manifestations could be attributed to this finding. After tapering of the i.v. NTG dose, the arterial methemoglobin level rapidly returned to 0. A determination of the major methemoglobin-reducing enzyme, NADH ferricyanide reductase,*[8] revealed it to be in the normal range (patient 21.4, control 15.3, normal 19.2 ± 3.8), thus excluding the possibility of a congenital enzyme deficiency. The elevated methemoglobin level in this patient may have been the result of the simultaneous administration of i.v. NTG and phenazopyridine (Pyridium®), which is an aniline dye whose use has been associated with methemoglobinemia.[9]

Discussion

Methemoglobinemia interferes with oxygen delivery in 2 ways: (1) In the oxidized form, hemoglobin cannot release or take up oxygen,[4] and (2) its presence shifts the oxyhemoglobin dissociation curve to the left.[5] A bluish

* NADH ferricyanide reductase assays were kindly performed by Dr. E. Beutler, Scripps Institute, La Jolla, California.

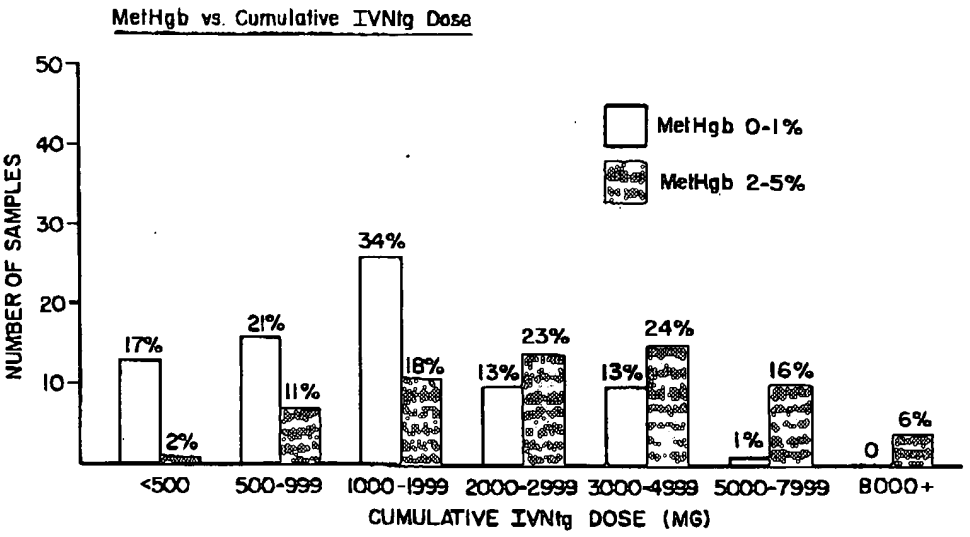

FIGURE 2. A comparison of total, cumulative dose of intravenous nitroglycerin (IVNtg) received and number of normal vs abnormal methemoglobin (MetHgb) samples. A modified logarithmic scale is used for cumulative IV NTG dose in order to make the number of samples in each range comparable. The numbers above the bars refer to the percentage of all normal or abnormal samples in that range of doses.

discoloration of the skin occurs at total methemoglobin levels of 1.5 g. When 30% of hemoglobin is present as methemoglobin, mild fatigue, lethargy, headache and a decrease in exercise tolerance occur. When methemoglobin levels reach 60%, symptoms of inadequate tissue oxygenation occur such as dyspnea, coma or convulsions. The lethal level of methemoglobin in humans is above 70%.[10] However, the additive effects of coexistent anemia, hypoxemia and decreased cardiac output must also be considered and in these circumstances patients could become symptomatic at lower levels.

The metabolism of NTG occurs both in the liver and at various peripheral sites, where it is metabolized by a glutathione reductase, resulting in the formation of a nitrite.[11] Nitrites convert oxyhemoglobin to methemoglobin.[4,12]

Oxyhemoglobin and methemoglobin normally occur in equilibrium in the body in a ratio of 99 to 1. This ratio may be altered by agents that increase the rate of oxidation (nitrates, sulfonamides, aniline dye derivatives) or in patients that are deficient in the enzyme necessary for reducing methemoglobin.[9,13,14]

Although NTG-induced methemoglobinemia has been reported,[1–3] the incidence and significance of this finding has been questioned in patients receiving clinically effective doses of nitrates.[15,16] The results from our study suggest that clinically significant methemoglobinemia is rare when the usual doses of i.v. NTG are used. Patients who receive i.v. NTG have higher than normal arterial methemoglobin levels, and these levels are positively correlated with the amount of i.v. NTG received; however, none of our patients had levels that approached those necessary to cause symptoms. Nevertheless, the development of abnormally elevated methemoglobin levels can reduce oxygen-carrying capacity and, thus, potentially precipitate or aggravate tissue ischemia.

In conclusion, clinically significant methemoglobinemia associated with i.v. NTG administration is uncommon; however, it should be considered when large amounts of NTG are administered, especially in association with other oxidizing agents.

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